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Association of ozone with mortality and emergency room visits for cardiovascular and respiratory diseases in Seoul, Korea

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Association of ozone with mortality and emergency room visits for cardiovascular and respiratory disease in Seoul, Korea

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이 논문을 보건학 석사학위논문으로 제출함

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Abstract

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Background: Ground-level ozone is known to cause acute health effects on mortality, emergency room (ER) visits and hospital admission. Many previous studies have shown significant positive associations with non-accidental, cardiovascular and respiratory mortality and relatively fewer studies have examined the effect of ozone on ER visits in Seoul, Korea. Further, the shapes of concentration-response (C-R) relationship with mortality showed inconsistent results and the relationship with ER visits has never been explored.

Objectives: The purpose of this study is to examine the effect of ozone on cardiovascular and respiratory diseases and to explore the shapes of the C-R relationship with mortality and ER visits.

Methods: Time series analyses with generalized linear model (GLM) were used to estimate the effect of ozone. We constructed natural spline model of ozone to explore the shapes of the associations and compared Quasi-Akaike Information Criterion (QAIC) between natural spline model and linear model. We chose either a spline model or a linear model for each health outcome with the shape of the C-R relationship and QAIC. To estimate the effect of short-term exposure to ozone, excessive relative risk (ERR) was computed. We also performed age- and sex-stratified analyses and respiratory-specific diseases analyses.

Results: We found a significant non-linear relationship of ozone with cardiovascular mortality, while a linear relationship with respiratory ER visits. Ozone showed adverse effects on cardiovascular mortality (ERR = 1.36%, 95% CI: 0.422 - 2.311), respiratory ER visits (1.869%, 95% CI: 0.739 - 3.011), asthma ER visits (6.267%, 95% CI: 3.846 - 8.744), COPD ER visits (3.707%, 95% CI: 1.673 - 5.781) and pneumonia ER visits (3.150%, 95% CI: 1.847 - 4.469). Moreover, we found cardiovascular mortality and ER visits had significantly higher risk on people above 65 years old (1.170%, 95% CI: 0.098 - 2.258, 1.769, 95% CI: 0.340 - 3.218) and respiratory ER visit also had higher risk on people above 65 years (1.845%, 95% CI: 0.316 - 3.397) and male (1.884%, 95% CI: 0.735 - 3.047).

Conclusion: Our results confirmed the non-linear relationship between ozone and cardiovascular mortality with the existence of a threshold. However, the association between ozone and ER visits showed a linear relationship rather than non-linear. Further, the findings of estimated risk indicate that the impact of ozone on respiratory diseases could trigger ER visits, while leading to death on cardiovascular diseases.

Keywords : ozone, mortality, emergency room visits, cardiovascular disease, respiratory disease, generalized linear model

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Chapter 1. Introduction

1.1 Background

Ground-level ozone is a common air pollutant hazardous to living organisms on Earth. Ozone in troposphere (referred to as ozone herein) is a secondary air pollutant formed by photochemical reaction between nitrogen oxides (NOx) and volatile organic compounds (VOCs) with sunlight (WHO 2000, WHO 2006). Also formation of ozone is more active at high ambient temperature and in densely populated regions such as urban and metropolitan areas. Unexpectedly, ozone is naturally added to the atmosphere, but excessive addition by human is the problem that causes adverse effects on human health. Thus due to the rapid economic development, air pollutant became an important public health issue. Since then, ozone was identified as an air pollutant in human health through the Clean Air Act (CAA) by U.S. Environmental Protection Agency (EPA) (Hubbell, Hallberg et al. 2005). So even the mechanism of exposure to ozone remains uncertain, number of epidemiological studies and human studies reported that ozone mostly reaches the lower respiratory tract and causes respiratory-related health effects such as induction of respiratory symptoms, decrements of lung function and inflammation of respiratory tract (Spektor, Lippmann et al. 1988, McDonnell, Stewart et al. 1999, Schwarzenegger 2005, Filippidou and Koukouliata 2011). It also reported that even with healthy young adults, repeated and continuous exposure to ozone could cause vulnerability of respiratory system and lung functions.

Exposure to ozone has affected human health: mortality, emergency room (ER) visits, hospital admissions and medication in the past decades. One of the representative episodes of air pollutant was London smog in 1952 (Wilkins 1954, Anderson, de Leon et al. 1996). Ozone is known as a primary component of smog and it consistently showed positive associations with daily mortality (Anderson, de Leon et al. 1996). Likewise, an European meta-analysis studies conducted by WHO reported that the risk increased is in non-accidental, cardiovascular and respiratory mortality in relation to ozone (Anderson, Atkinson et al. 2004). Similar association is shown in a previous study in U.S., which provides a strong evidence of the association between ozone and mortality, especially larger effects for cardiovascular and respiratory mortality (Bell, Dominici et al. 2005). Substantial studies on the association with ER visits or hospital admission have assessed and most of the studies examined the effect on respiratory diseases (Cody, Weisel et al. 1992, Burnett, Brook et al. 1997, Gent, Triche et al. 2003). The effect of ozone was reported to cause asthma (Cody, Weisel et al. 1992), pneumonia (Schwartz 1994) and chronic obstructive pulmonary disease (COPD) (Anderson, Spix et al. 1997, Medina-Ramón, Zanobetti et al. 2006), especially on children and the elderly. In Korea, there have been a few studies on the effect of ozone on morbidity and some studies reported the risk of ozone is increased among children under 15 years old (Lee, Kim et al. 2002) and elderly populations (Lee, Kim et al. 2003).

Furthermore, several studies have shown non-linearity of concentration-response (C-R) relationships of ozone with the existence of a threshold. Since the effect of temperature is known to be the non-linear relationship with health response and ozone concentration is highly correlated with temperature, considering the relationship of ozone as linear is a highly strong assumption. A limited number of studies in Korea found non-linear relationship with non-accidental mortality during the warm season (Kim, Lee et al. 2004, Bae, Lim et al. 2015). However, results of the other studies in different countries have insufficient evidence for the shapes of the association (Bell, Peng et al. 2006, Hazucha and Lefohn 2007, McDonnell, Stewart et al. 2012).

Based on the earlier studies, there were significant positive associations with non-accidental and cardiorespiratory mortality and relatively fewer studies have investigated the effect on ER visits with ozone in Seoul, Korea. Further, the shapes of C-R relationships with mortality showed inconsistent results and the relationship with ER visits has not been explored. Due to the lack of consistency between previous studies, it would be meaningful to examine the relationships both with mortality and ER visits.

1.2 Objectives

The objectives of this study are

(1) to examine the effect of ozone on cardiovascular and respiratory disease with mortality and emergency room visits and

(2) to explore the shapes of the relationship with ozone on mortality and emergency room visits in Seoul, Korea.

Chapter 2. Material and Methods

2.1 Data

2.1.1 Study period

The study included mortality and ER visits data as the health outcomes and the study periods were from 1 January, 2000 to 31 December, 2013 and from 1 January, 2010 to 31 December, 2013, respectively. Since ozone concentrations are higher during the summer, we focused our analyses during the warm season from April to September.

Health outcome data	Study period
Mortality	2000 - 2013
Emergency room (ER) visits	2010 - 2013

2.1.2 Mortality data

The mortality data were obtained from The Korea National Statistical Office. The causes of deaths were classified by cardiovascular disease (I00-I99) and respiratory diseases (J00- J99) according to the International Classification of Disease, 10th revision (ICD-10). The subcategories of respiratory disease included asthma (J45-J46), chronic obstructive pulmonary disease (COPD) (J40-J44) and pneumonia (J09-J22). Also we stratified cardiovascular and respiratory death by age (below and above 65 years) and sex.

2.1.3 Emergency room visits data

Data on ER visits were provided by National Emergency Medicine Center (NEMC). NEMC established a standard system of emergency information to manage ER visits patients called National Emergency Department Information System (NEDIS). NEDIS was established on 2004 and began with 16 regional emergency medical centers and number of emergency centers in Seoul were added to the system until 2009. 29 emergency medical centers in Seoul were consistently enrolled in NEDIS from 2009 to 2013. The diagnosis of cardiovascular and respiratory disease including asthma, COPD, pneumonia were classified by ICD-10. Same as mortality, cardiovascular and respiratory ER visits were stratified by age (below and above 65 years) and sex.

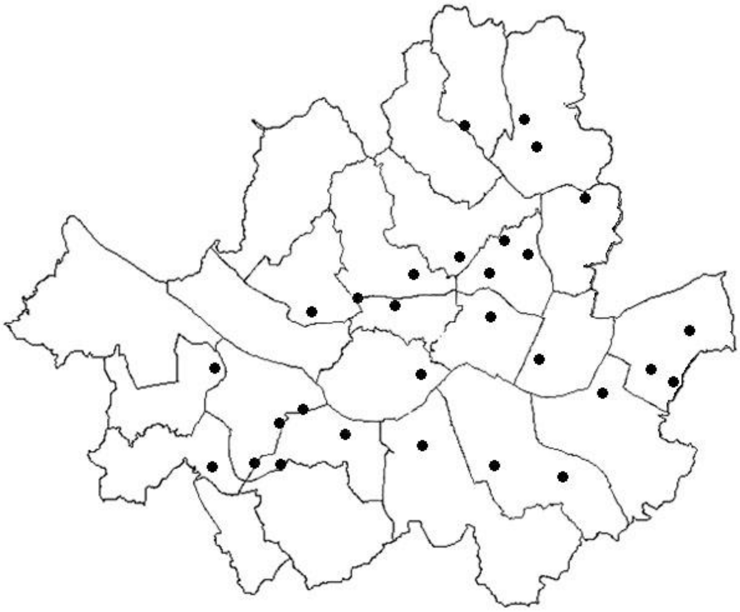


Figure 1. The location of 29 emergency medical centers in Seoul, Korea

2.1.4 Air pollutant data

The air pollutant data collected at the monitoring stations were ozone (O_3), particulate matter ≤10μm in aerodynamic diameter (PM_{10}), nitrogen dioxide (NO_2) and sulfur oxide (SO_2) and these were provided by Korea Meteorological Office and Research Institute of Public Health. The daily concentration of air pollutants were continuously measured at the monitoring station. Daily mean concentrations were computed as daily 8-hour averages (from 9 am to 5 pm) for ozone and daily 24-hour averages for other pollutants. The maximum ozone concentration was the highest hourly level between 9 am and 5 pm and maximum temperature was the highest hourly level of the day.

2.1.5 Meteorological data

The meteorological data including daily mean temperature (℃), maximum temperature (℃) and relative humidity (%) were obtained from the Korea Meteorological Office. The daily average were computed through hourly data of each station.

2.2 Statistical analyses

2.2.1 Basic model

We used time series analyses using generalized linear model (GLM) with quasi-poisson regression to estimate the effect of ozone (Bhaskaran, Gasparrini et al. 2013). In the model, we adjusted temperature, relative humidity, PM_{10}, day of the week (DOW), holiday, and time trend as confounders. To control the effect on the previous day of ozone level, we used 2-day moving average (lag 0 and lag 1) and used current day average for other environmental variables including temperature, humidity and $PM_{10.}$

The general model as follows:

$$\boldsymbol{log\big(E(Y_t)\big) = ns(O_3)\ or\ O_3\ + ns(temperature) + humidity + PM_{10}}$$
$$\boldsymbol{+ DOW + holiday + ns(time, df\ = 3/yr)}$$

where Y_t is the daily number of death or ER visits for cause-specific disease at day t; $ns()$ refers to the natural spline function; $O_3, temperature, humidity$ and PM_{10} refer to the daily average; DOW is day of the week; $holiday$ is a dummy variable with the value of 1 if the day was a public holiday; $time$ represents the long-term temporal trend with 3 df (degree of freedom) per year. The df of time trend was selected based on the previous studies 3 or 4 df per year for the warm season. We also fitted smoothing function for daily temperature and ozone was added into the model as a smoothing term or a linear term depending on the health outcomes.

Data step for daily time series data was conducted using SAS 9.4.

2.2.2 Model selection

We constructed a natural spline model of ozone and explored the shapes of the concentration-response (C-R) relationship of ozone on mortality and ER visits with 95% confidence interval (CI). Additionally, we compared Quasi-Akaike Information Criterion (QAIC) between the natural spline model and the linear model (Daniels, Dominici et al. 2000, Bae, Lim et al. 2015). AIC is a fundamental method for the statistical model selection and QAIC is for quasi-likelihood model, which was used in the study (Taper 2004). The preferred model is with a lower QAIC.

$$\mathrm{QAIC} = \frac{-2\log(L\ (model))}{\hat{c}} + 2\ K$$

where $L(model)$ is the likelihood of the model; $\hat{c}$ is the overdispersion parameter; K is the number of parameters. Without overdisperion, $\hat{c}$ equals 1, then QAIC becomes equal to AIC. According to the results of C-R relationship and QAIC, we selected either the natural spline model or the linear model for each health outcome. If the natural spline model was selected, the threshold was estimated at the minimum relative risk.

QAIC analysis was performed with the package 'MuMIn' in R version 3.1.2.

2.2.3 Excessive relative risk (ERR)

From the basic model, the effects of ozone were estimated by the excessive relative risk (ERR) for 10 ppb increase in daily 8-hour average ozone concentration.

$$\mathrm{RR} = e^{\beta*10}$$

$$\mathrm{ERR} = (\mathrm{RR} - 1) * 100$$

$$95\%\ \mathrm{CI} = e^{((\beta \pm 1.96\ SE)*10\ )}$$

For the natural spline model with the estimated threshold, we calculated the ERR for 10 ppb increase above the threshold and its 95% CI.

Chapter 3. Results

3.1 Descriptive statistics

Table 1 to 3 show the descriptive statistics of air pollutant, meteorological variables, daily number of death and daily number of ER visits in all seasons and for in the warm season in Seoul, Korea. From 2000 to 2013 during the warm season, 8-hour average ozone concentration was 31.34 ppb and daily mean temperature was 20.97 ℃. The daily number of cardiovascular death was 22.99 and respiratory death was 5.38. Cardiovascular and respiratory deaths were higher for people above 65 years and similar number of deaths between male and female. During the warm season, the daily number of asthma, COPD and pneumonia were 0.80, 1.55 and 1.76, respectively. For the mean number of ER visits, cardiovascular diseases were 169.94 and respiratory diseases were 462.05 on average. Asthma, COPD and pneumonia were 14.81, 21.14, and 114.07, respectively. Since death is the least common events, daily number of ER visits was higher for both cardiovascular and respiratory diseases.

Figure 4 shows the distribution of daily number of death and ER visits for cardiorespiratory diseases by each weekday. The number of daily deaths did not show a great difference on each day of the week, while ER visits showed the higher average number of visits on Sundays when hospitals are closed.

Table 1. Summary statistics of air pollutants and weather variables from 2000 to 2013 in Seoul, Korea.

		All-season						Warm season					
		N	Mean	SD	Min.	Median	Max.	N	Mean	SD	Min.	Median	Max.
Air pollutants	O_3 (ppb)[a]	5114	24.03	13.81	1.48	22.00	91.83	2562	31.34	14.21	2.51	30.69	91.83
	max O_3 (ppb)[b]	5114	35.03	20.07	1.88	31.52	143.19	2562	45.62	21.13	3.19	44.22	143.19
	PM_{10} ($\mu g/m^3$)	5114	58.45	42.24	4.99	50.56	1016.43	2562	53.03	42.82	5.64	45.84	1016.42
	NO_2 (ppb)	5114	35.44	12.59	6.45	33.77	92.16	2562	31.67	10.98	6.45	30.07	78.80
	SO_2 (ppb)	5114	5.36	2.24	1.95	4.81	22.67	2562	4.43	1.52	1.95	4.03	15.29
Weather variable	Temperature (℃)	5114	12.71	10.44	-15.72	14.20	31.78	2562	20.97	5.31	3.91	22.09	31.78
	Humidity (%)	5114	61.11	14.75	19.42	61.04	96.25	2562	65.48	14.86	21.08	66.55	96.00

a: Daily 8-hour average (9 am-5 pm)

b: Daily maximum 8-hour average

Table 2. Summary statistics of mortality of non-accidental, cardiovascular and respiratory disease from 2000 to 2013 in Seoul, Korea

		All-season						Warm season					
		N	Mean	SD	Min.	Median	Max.	N	Mean	SD	Min.	Median	Max.
Mortality (2000-2013)	Non-accidental	5114	94.997	12.14	55	95	148	2562	90.784	10.99	55	90	145
	< 65 years	5114	30.308	6.66	12	30	58	2562	29.53	6.52	12	29	56
	≥65 years	5114	64.689	11.22	28	64	108	2562	61.254	10.23	28	61	103
	male	5114	51.529	8.09	28	51	88	2562	49.669	7.74	28	49	82
	female	5114	43.468	7.62	19	43	82	2562	41.116	6.92	19	41	69
	Cardiovascular	5114	23.947	5.69	8	24	45	2562	22.462	5.39	8	22	45
	< 65 years	5114	5.863	2.83	0	6	21	2562	5.565	2.69	0	5	17
	≥65 years	5114	18.085	4.69	4	18	37	2562	16.897	4.43	4	17	35
	male	5114	12.038	3.7	3	12	29	2562	11.298	3.56	3	11	27
	female	5114	11.909	3.78	1	12	27	2562	11.164	3.58	2	11	24
	Respiratory	5114	6	2.81	0	6	21	2562	5.674	2.65	0	5	19
	< 65 years	5114	0.812	0.94	0	1	8	2562	0.776	0.91	0	1	8
	≥65 years	5114	5.188	2.64	0	5	18	2562	4.898	2.5	0	5	18
	male	5114	3.408	1.97	0	3	14	2562	3.273	1.9	0	3	12
	female	5114	2.592	1.77	0	2	14	2562	2.4	1.65	0	2	12
	Asthma	5114	0.804	0.96	0	1	7	2562	0.74	0.91	0	1	7
	COPD	5114	1.588	1.29	0	1	9	2562	1.526	1.24	0	1	7
	Pneumonia	5114	2.2	1.85	0	2	12	2562	2.036	1.77	0	2	12

COPD: chronic obstructive pulmonary disease

Table 3. Summary statistics of ER visits of cardiovascular and respiratory disease from 2010 to 2013 in Seoul, Korea

		All-season						Warm season					
		N	Mean	SD	Min.	Median	Max.	N	Mean	SD	Min.	Median	Max.
ER visits (2010-2013)	Cardiovascular	1461	170.57	24.48	99	169	260	732	169.94	23.83	119	168	254
	< 65 years	1461	267.10	125.96	111	229	1247	732	275.73	119.30	119	236	835
	≥65 years	1461	31.00	9.52	9	29	94	732	29.78	7.96	12	29	56
	male	1461	162.12	67.89	25	144	656	732	169.22	63.21	77	150	461
	female	1461	131.55	63.61	29	114	685	732	133.84	56.91	50	117	406
	Respiratory	1461	451.84	211.52	208	384	2253	732	462.05	195.52	209	393.5	1357
	< 65 years	1461	267.10	125.96	111	229	1247	732	275.73	119.30	119	236	835
	≥65 years	1461	31.00	9.52	9	29	94	732	29.78	7.96	12	29	56
	male	1461	162.12	67.89	25	144	656	732	169.22	63.21	77	150	461
	female	1461	131.55	63.61	29	114	685	732	133.84	56.91	50	117	406
	Asthma	1461	15.36	6.48	2	14	66	732	14.81	6.84	2	14	66
	COPD	1461	21.64	9.31	4	20	88	732	21.14	8.69	7	20	65
	Pneumonia	1461	128.01	62.54	39	114	633	732	114.07	47.25	39	105	374

COPD: chronic obstructive pulmonary disease

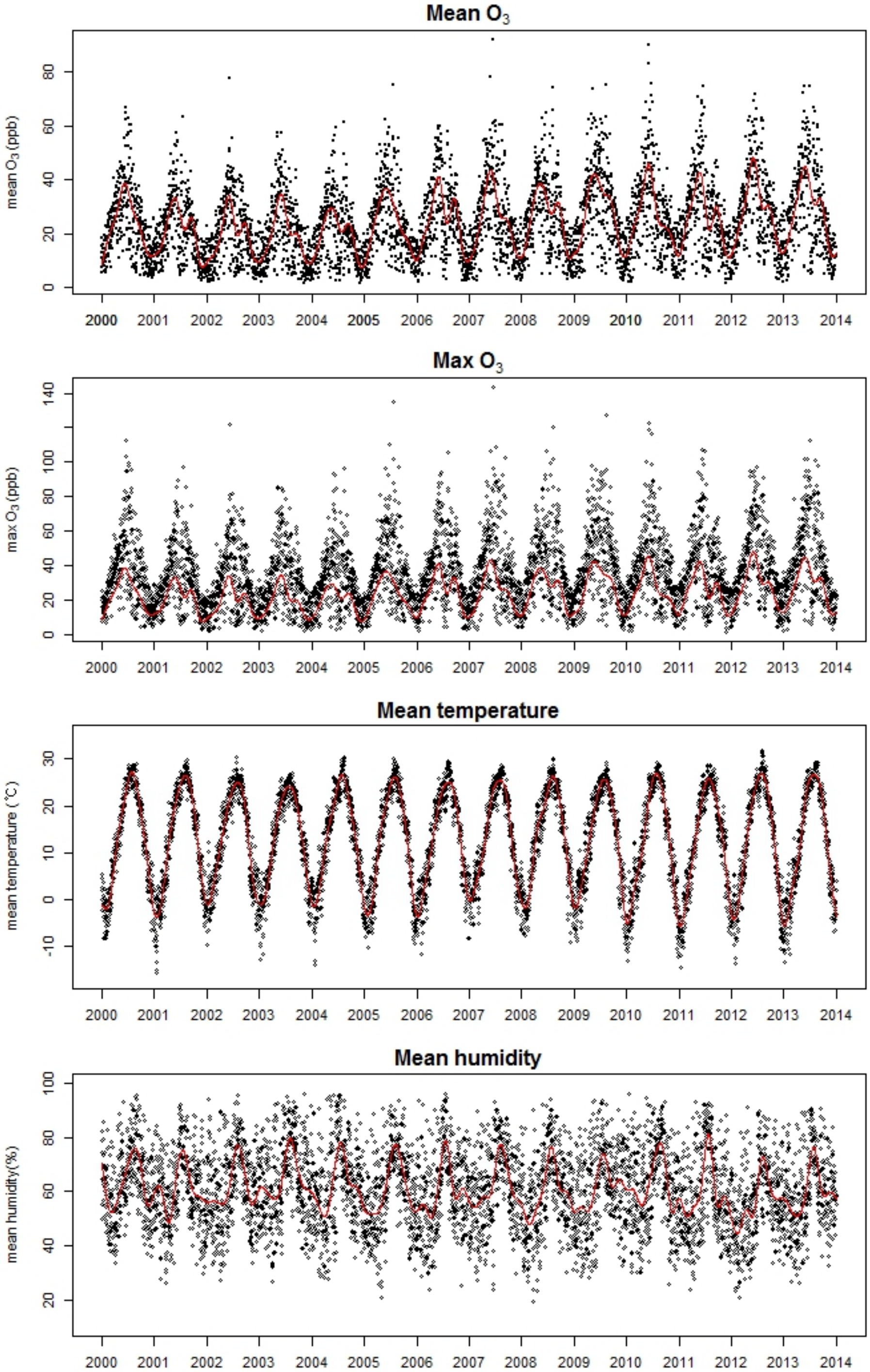


Figure 2. Time-series plot of mean ozone, maximum ozone, mean temperature and mean humidity from 2000 to 2013 in Seoul, Korea

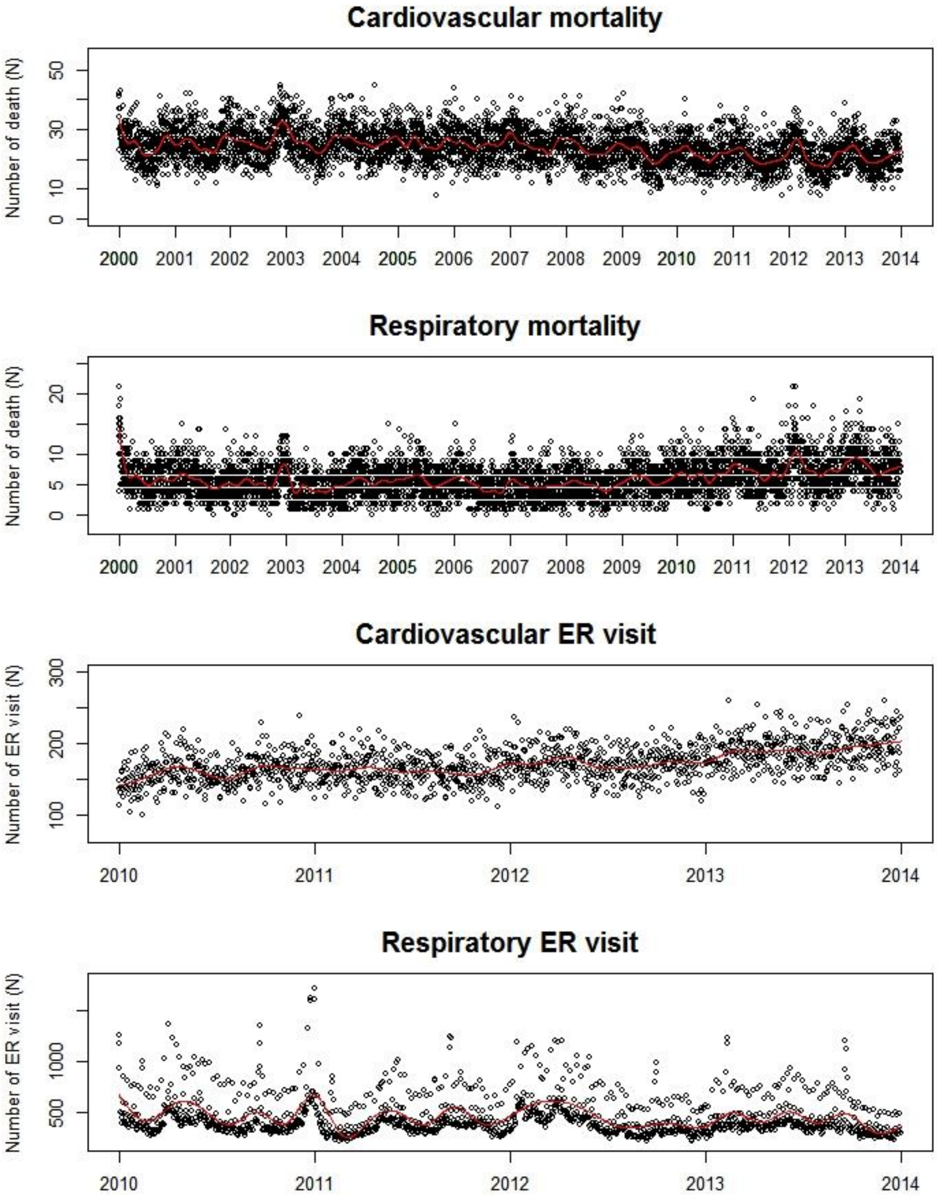


Figure 3. Time-series plot of daily number of death (2000-2013) and ER visits (2010-2013) for cardiovascular and respiratory diseases in Seoul, Korea

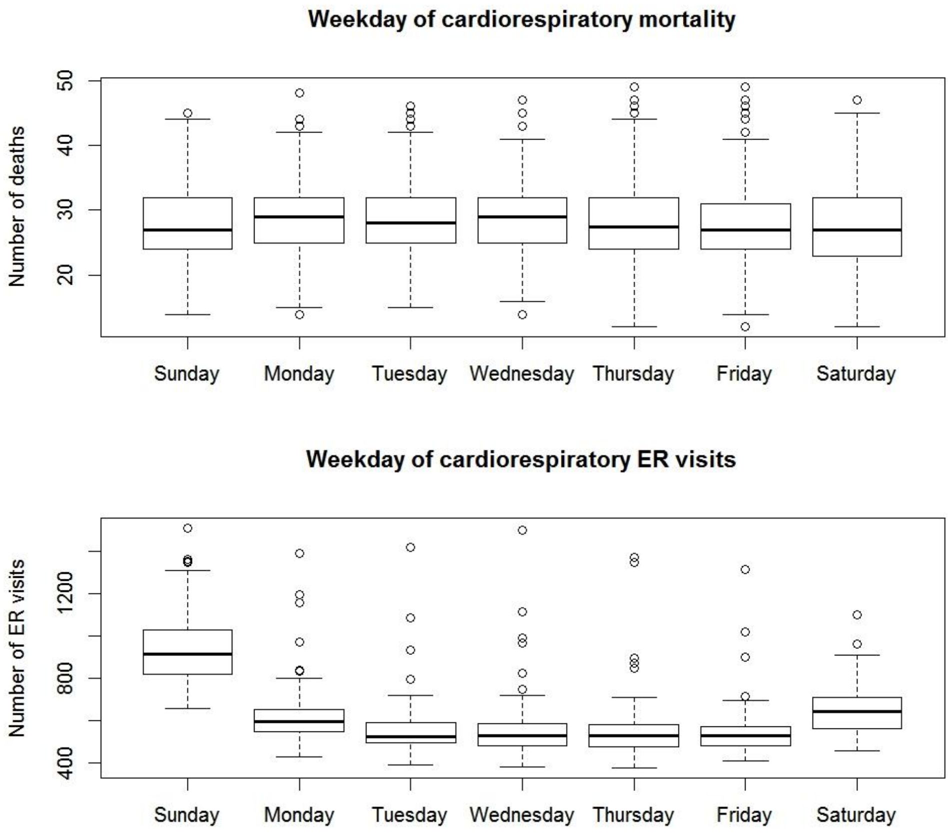


Figure 4. Distributions of daily number of death (2000-2013) and ER visits (2010- 2013) of cardiorespiratory diseases for weekdays in Seoul, Korea

3.2 Association of ozone with mortality and emergency room visits

We examined the relationships of ozone with mortality and ER visits using the natural spline model. Figure 5 and 6 show C-R relationship of ozone on mortality and ER visits with 95% CI. Table 4 shows the comparison of QAIC between the natural spline model and the linear model for each of the health outcomes: cardiovascular mortality, respiratory mortality, cardiovascular ER visits and respiratory ER visits.

As the results of C-R relationship, the cardiovascular mortality clearly showed a non-linear relationship with the presence of a threshold, while the other health outcomes (respiratory mortality, cardiovascular ER visits and respiratory ER visits) did not show any U or J shape, rather more close to the linear model. Smaller QAIC suggests the better fit of the model, so if the comparison of △QAIC (linear model QAIC – natural spline model QAIC) between the natural spline model and the linear model is negative, the natural spline model has the better fit. From table 4, cardiovascular mortality had a negative △QAIC (-8.8) supporting nonlinearity between ozone and cardiovascular mortality. Combining the results of the shape of the C-R relationship and QAIC, cardiovascular mortality supported non-linearity with ozone, while respiratory mortality and ER visits suggested that the linear relationship was appropriate for assessing the effect of ozone.

Figure 7 shows the overall association of ozone with mortality and ER visits for cardiovascular and respiratory disease. From the preceding results, cardiovascular mortality used the natural spline model with a threshold, while respiratory mortality, cardiovascular ER visits and respiratory ER visits used the linear models. The threshold of minimum relative risk for cardiovascular mortality was 26.508 ppb of daily 8-hour average ozone concentration.

We also performed sensitivity analysis with daily 8-hour maximum ozone concentration. Appendix 3 shows the shape of the C-R relationship with daily maximum ozone level and the shape showed a non-linear relationship with the presence of threshold. The threshold was 33.508 ppb, which was greater than the daily 8-hour average. Appendix 4 and 5 show the shapes of the C-R relationship with daily mean ozone and maximum ozone for non-accidental mortality. Both daily mean ozone and daily maximum ozone showed non-linear relationships with non-accidental mortality, which were consistent with the previous studies.

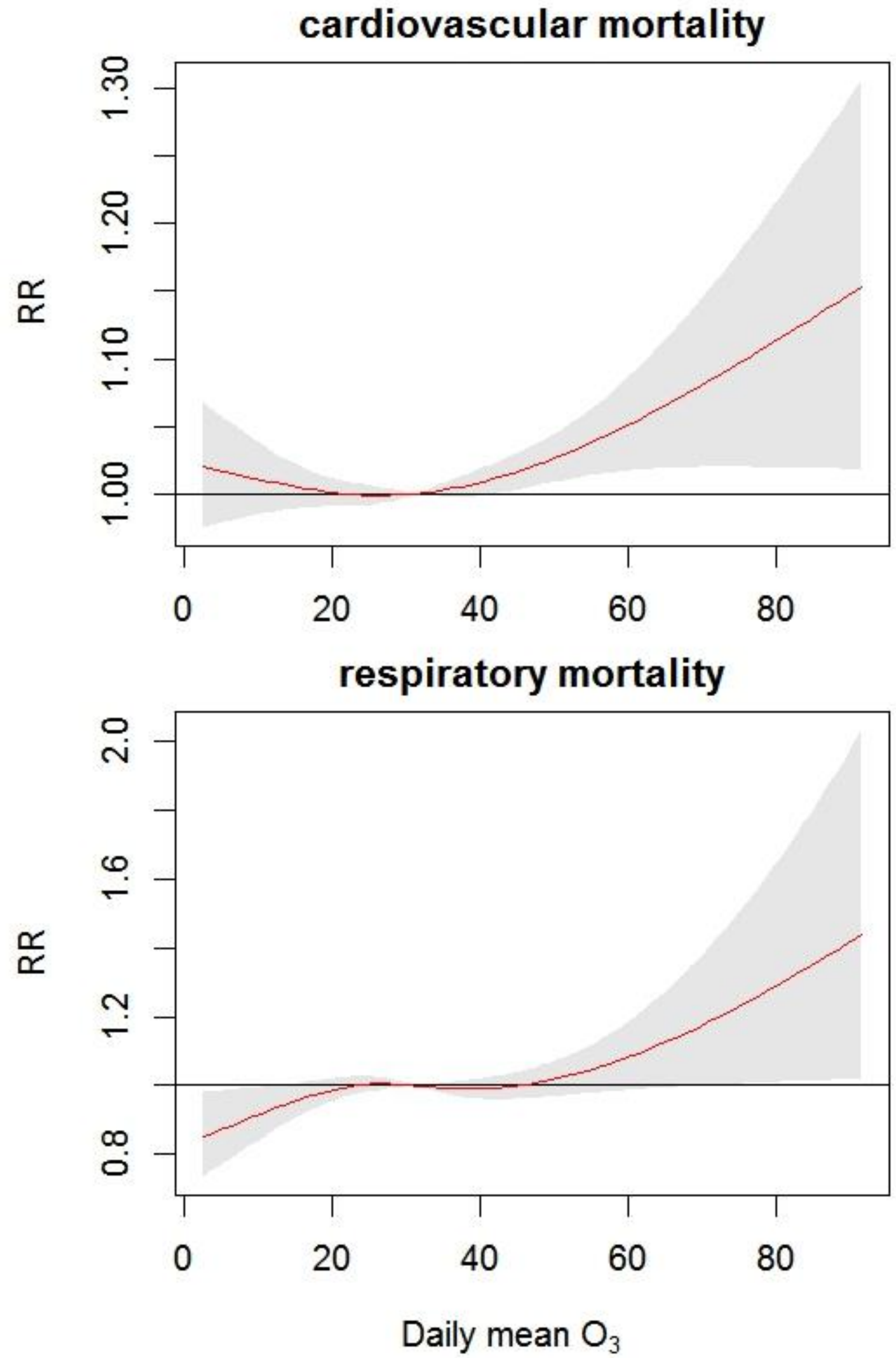


Figure 5. The estimated effect of daily mean ozone (lag0-1) on cardiovascular and respiratory mortality (2000-2013) with natural spine model Seoul, Korea

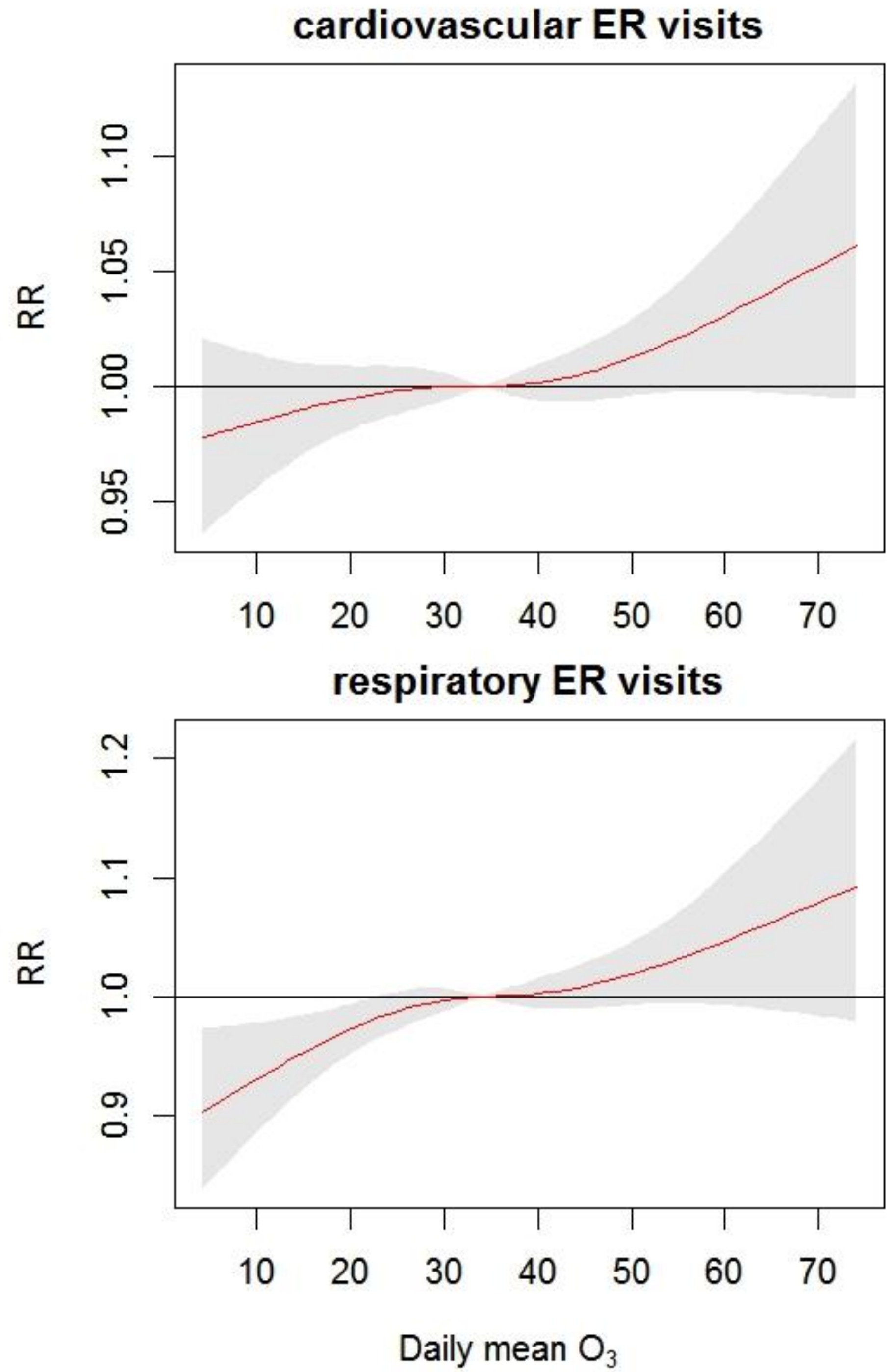


Figure 6. The estimated effect of daily mean ozone (lag0-1) on cardiovascular and respiratory ER visits (2010-2013) with natural spine model Seoul, Korea

Table 4. Comparison between natural spline model and linear model using QAIC

		Linear model				Natural spline model	Comparison
		beta	SE	p-value	QAIC	QAIC	△QAIC
Mortality	cardiovascular	7.05E-04	7.05E-04	0.023936	12688.27	12679.47	-8.8
	respiratory	0.0019627	0.0011967	0.010114	9878.161	9898.321	20.16
ER visits	cardiovascular	0.0007091	0.0004663	0.01287	4550.861	4558.363	7.50
	respiratory	0.0019089	0.0006674	0.004362	1297.811	1299.097	1.29

△QAIC: QAIC of linear model – QAIC of natural spline model

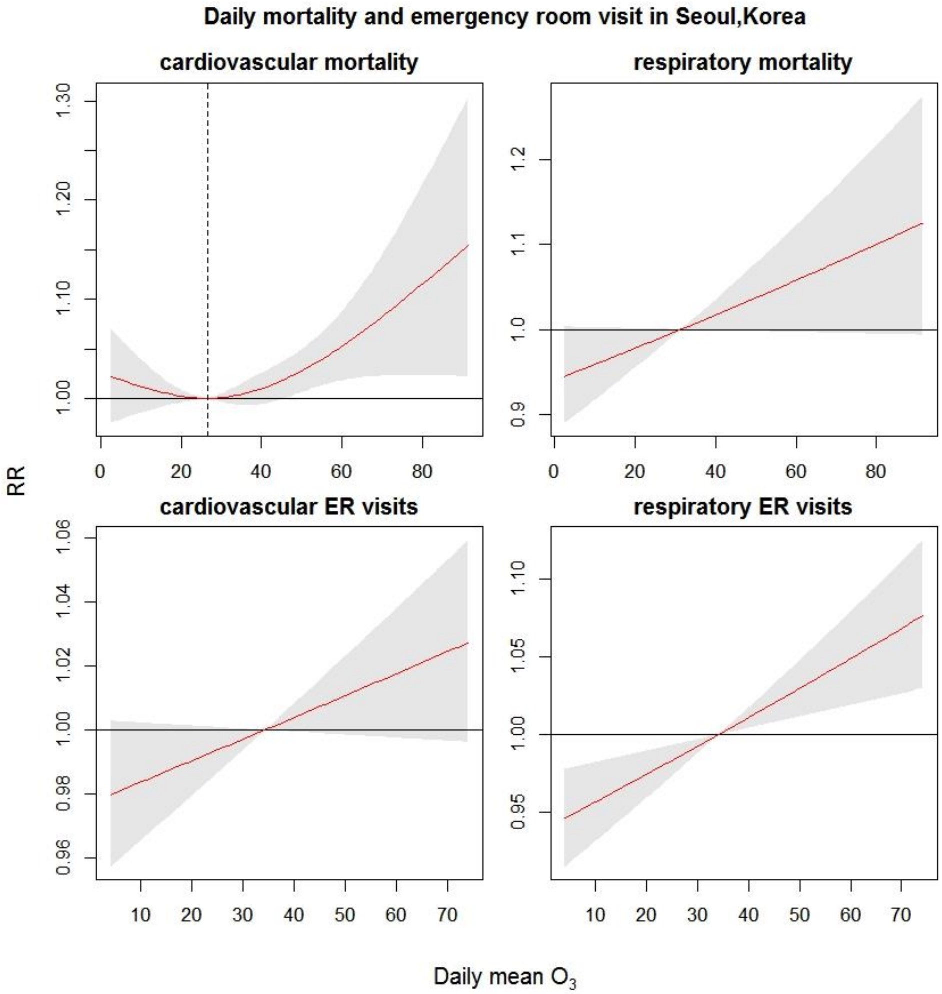


Figure 7. The overall estimated effect of daily mean ozone (lag0-1) on mortality and ER visits for cardiovascular and respiratory diseases in Seoul, Korea

Threshold of cardiovascular mortality: 26.508 ppb of daily 8-hour average ozone concentration

Figure 8 shows the association with respiratory-specific diseases: asthma, COPD and pneumonia. Comparing the results between mortality and ER visits, ER visits showed a steeper and clear linear C-R relationship than the relationship with mortality. Figure 9 to 12 show the association of ozone with stratification on age and sex. Cardiovascular mortality showed non-linear C-R relationships with both ages below and above 65 year old. However, for the sex-stratified analysis, female did not show the clear non-linearity. For ER visits, age- and sex-stratified analyses also implied the linear C-R relationship with ozone.

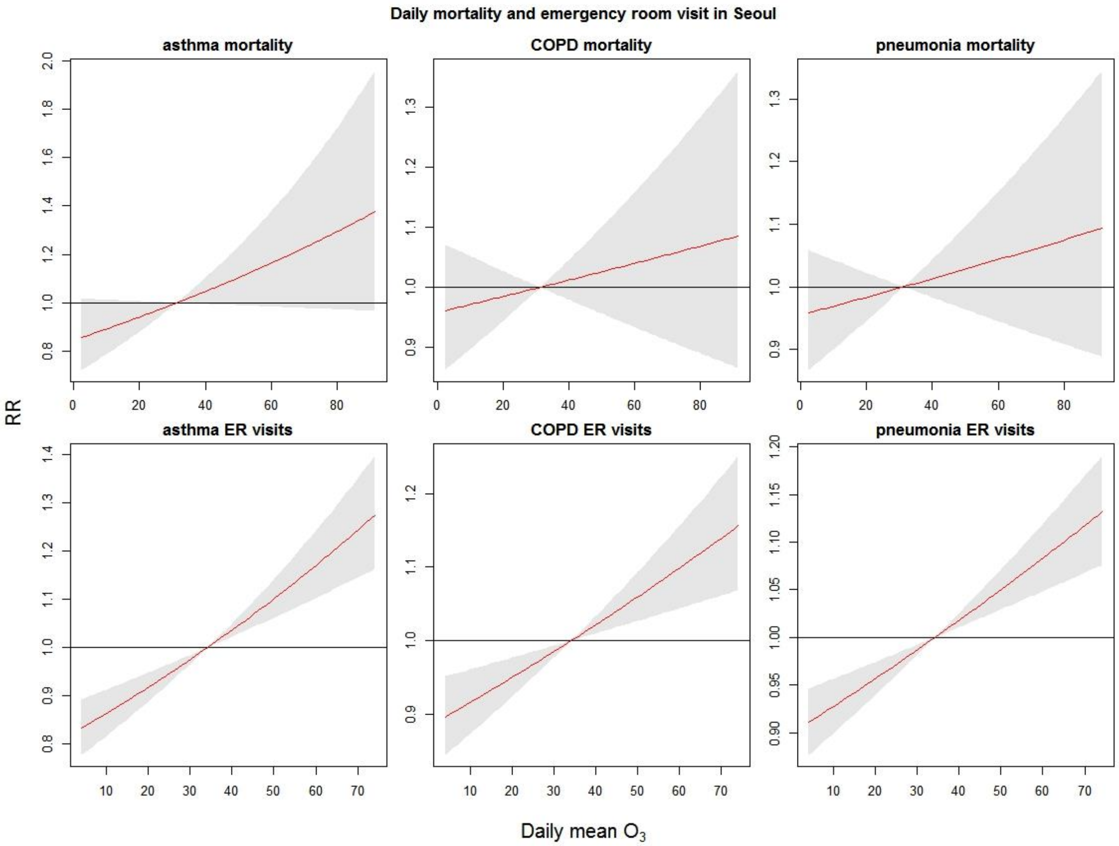


Figure 8. The estimated effect of daily mean ozone (lag0-1) on mortality and ER visits for asthma, COPD and pneumonia in Seoul, Korea

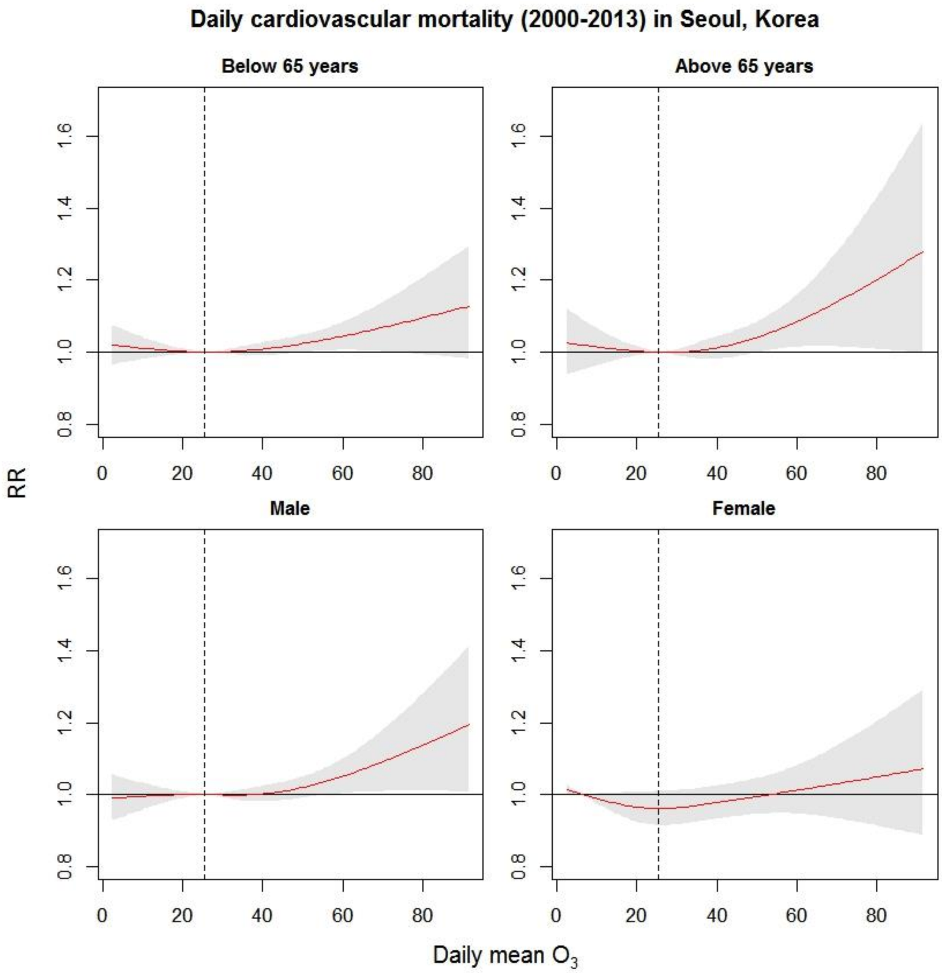


Figure 9. The estimated effect of daily mean ozone (lag0-1) on cardiovascular mortality with age and sex stratification

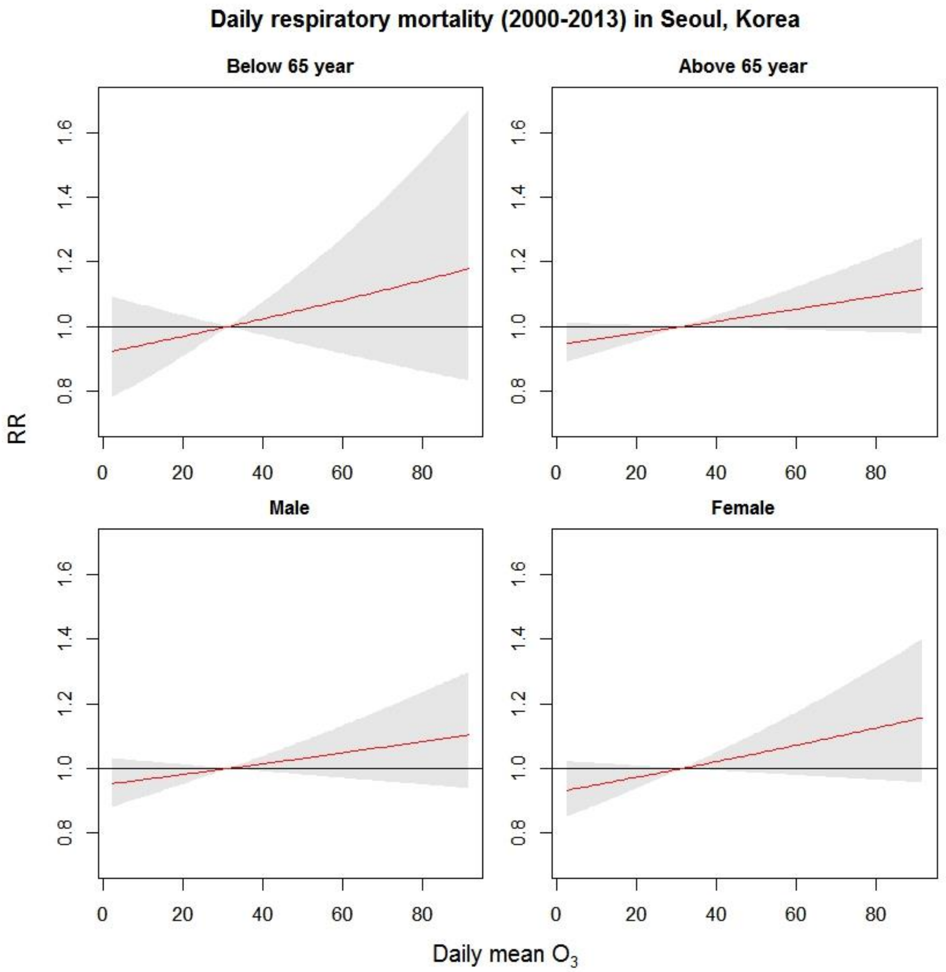


Figure 10. The estimated effect of daily mean ozone (lag0-1) on respiratory mortality with age and sex stratification

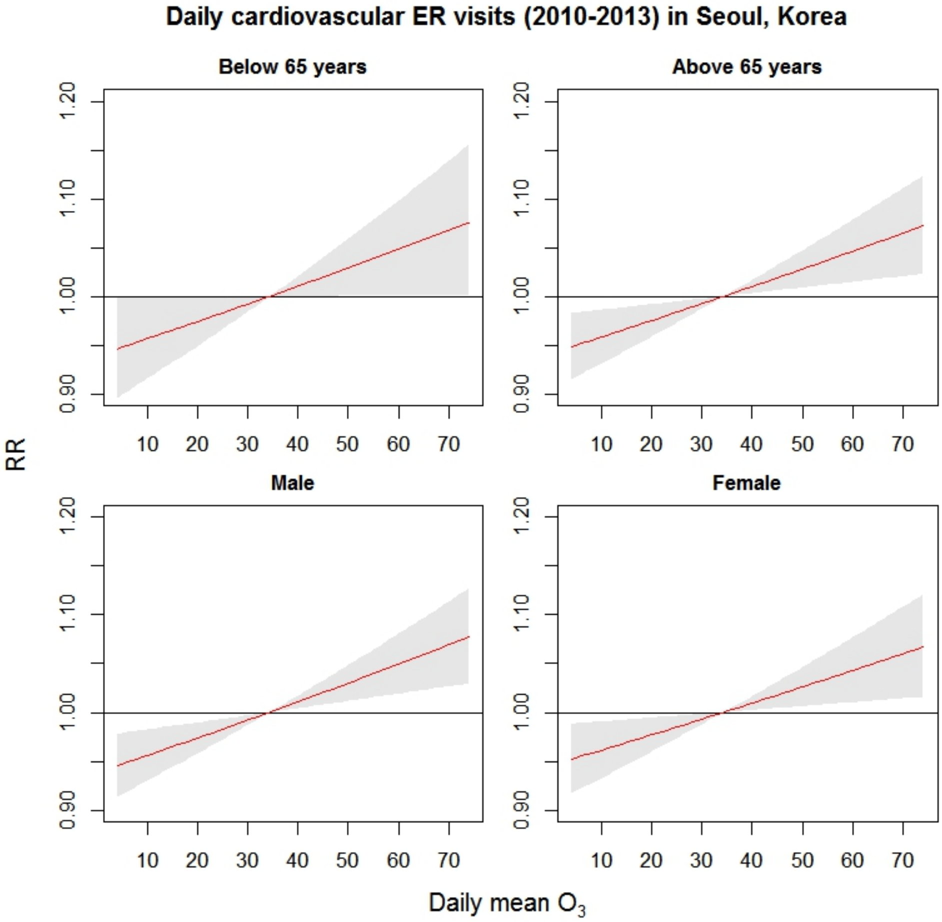


Figure 11. The estimated effect of daily mean ozone (lag0-1) on cardiovascular ER visits with age and sex stratification

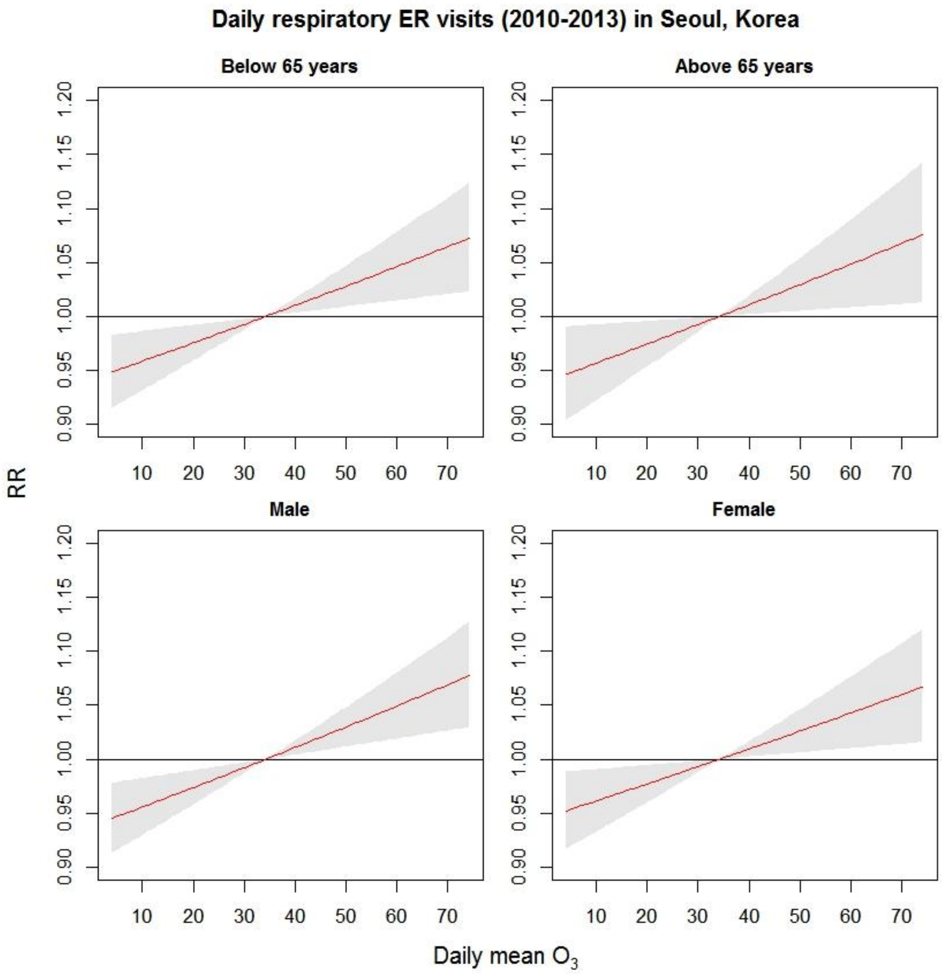


Figure 12. The estimated effect of daily mean ozone (lag0-1) on respiratory ER visits with age and sex stratification

3.3 Relative risk of cardiovascular and respiratory mortality and emergency room visits

Table 5 and figure 13 show the excessive relative risk (ERR) of mortality and ER visits for disease-specific health outcomes. Table 6, figure 14 and 15 show the results of age- and sex-stratified analyses. The excess risks was statistically significant on cardiovascular mortality, respiratory ER visits and respiratory-specific ER visits. Also age- and sex-stratified results were significant increases in risk of cardiovascular mortality, cardiovascular ER visits and respiratory ER visits. For mortality, ozone showed statistically significant effect on cardiovascular mortality with a 1.36% (95% CI: 0.422 - 2.311) increase in risk per 10 ppb increase in daily 8-hour average of ozone. Age- and sex-stratified analyses showed statistically significantly higher risk on age above 65 years old (2.010, 95% CI: 0.128 - 3.925) and female (1.610, 95% CI: 0.294 - 2.940). For ER visits, ozone was related to the risk increase of respiratory diseases and subcategories of respiratory diseases. A 1.869% (95% CI: 0.739 - 3.011) increase in risk was observed in respiratory ER visits and 6.267% (95% CI: 3.846 - 8.744), 3.707% (95% CI: 1.673 - 5.781), 3.150% (95% CI: 1.847 - 4.469) in asthma, COPD and pneumonia ER visits, respectively. Respiratory ER visits also showed the significant increase in risk of 1.766% (95% CI: 0.572 - 2.974) for age below 65 and of 1.845% (95% CI: 0.316 - 3.397) for age above 65 years. Also male showed a 1.884% (95% CI: 0.735 - 3.047) increase and female showed a 1.628% (95% CI: 0.130 - 3.149) increase in risk. In contrast to cardiovascular ER visits, age- and sex-stratified analyses showed significant results: above 65 years old (1.769, 95% CI: 0.340 - 3.218), male (1.693, 95% CI: 0.319 - 3.086) and female (1.628, 95% CI: 0.130 - 3.149).

Table 5. Relative risk and 95% CI associated with ozone for mortality and ER visits on cardiovascular and respiratory diseases

	subcategory disease	ERR	95% CI
Mortality			
Cardiovascular[a]		**1.360**	**(0.422, 2.311)**
Respiratory		1.975	(-0.110, 4.104)
	asthma	5.443	(-0.565, 11.813)
	COPD	1.372	(-2.358, 5.245)
	pneumonia	1.491	(-1.947, 5.049)
Emergency room visits			
Cardiovascular		0.679	(-0.095, 1.460)
Respiratory		**1.869**	**(0.739, 3.011)**
	asthma	**6.267**	**(3.846, 8.744)**
	COPD	**3.707**	**(1.673, 5.781)**
	pneumonia	**3.150**	**(1.847, 4.469)**

a: relative risk above threshold (25.508)

b: with 10 ppb increase of daily mean ozone

CI: confidence interval

Table 6. Relative risk and 95% CI associated with ozone for mortality and ER visits on cardiovascular and respiratory diseases with age and sex stratification

		ERR	95% CI
Mortality			
Cardiovascular			
	age < 65	**1.170**	**(0.098, 2.258)**
	age ≥65	**2.010**	**(0.128, 3.925)**
	male	1.110	(-0.192, 2.434)
	female	**1.610**	**(0.294, 2.940)**
Respiratory			
	age < 65	1.858	(-0.369, 4.136)
	age ≥65	2.777	(-3.011,8.911)
	male	1.667	(-1.054, 4.462)
	female	2.458	(-0.753, 5.772)
Emergency room visits			
Cardiovascular			
	age < 65	0.632	(-1.186, 2.484)
	age ≥65	**1.769**	**(0.340, 3.218)**
	male	**1.693**	**(0.319, 3.086)**
	female	**1.628**	**(0.130, 3.149)**
Respiratory			
	age < 65	**1.766**	**(0.572, 2.974)**
	age ≥65	**1.845**	**(0.316, 3.397)**
	male	**1.884**	**(0.735, 3.047)**
	female	**1.640**	**(0.391, 2.905)**

a: relative risk above threshold (25.508)
b: with 10 ppb increase of daily mean ozone
CI: confidence interval

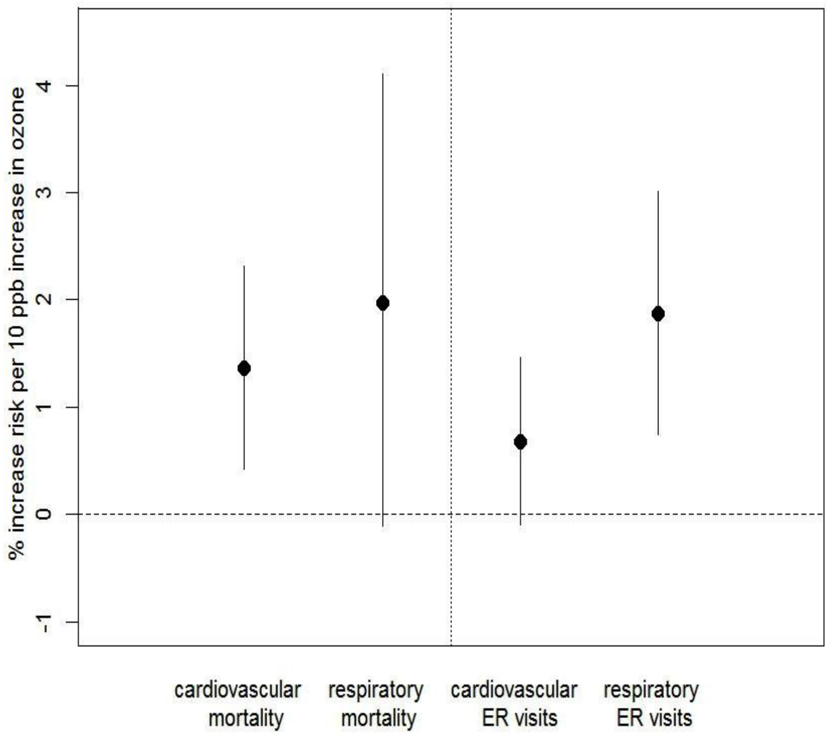


Figure 13. Percent increase of mortality and ER visits for cardiovascular and respiratory diseases with a 10ppb increase of ozone (lag0-1)

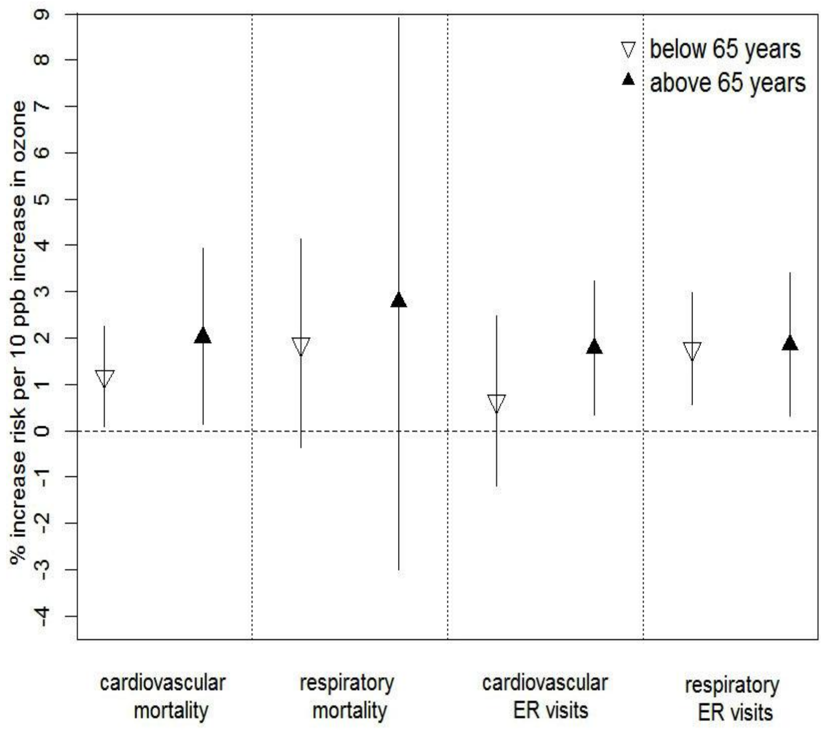


Figure 14. Percent increase of mortality and ER visits for cardiovascular and respiratory diseases with a 10ppb increase of ozone (lag0-1) with age stratification

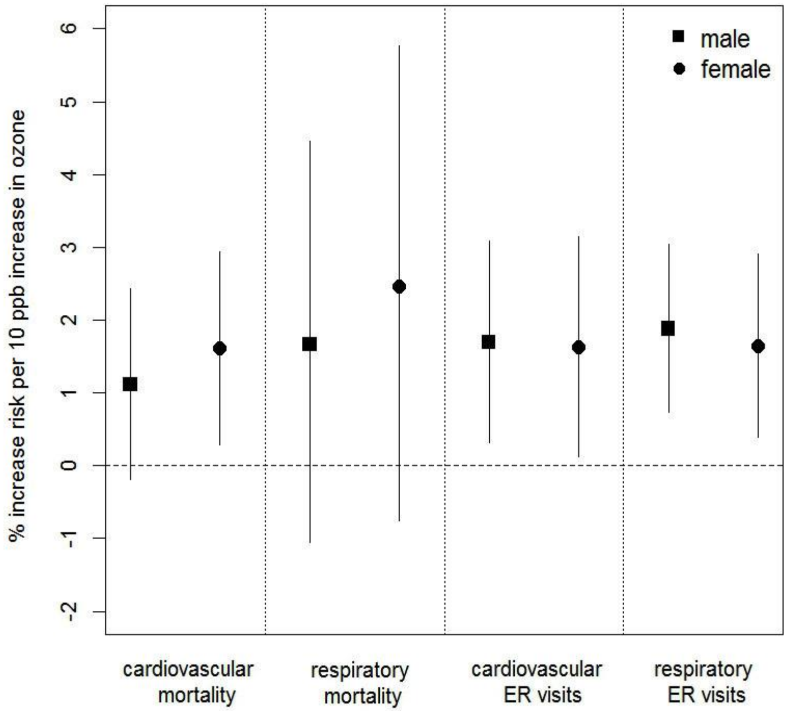


Figure 15. Percent increase of mortality and ER visits for cardiovascular and respiratory diseases with a 10ppb increase of ozone (lag0-1) with sex stratification

Chapter 4. Discussion

This study found significant associations of a short-term exposure to ozone with the cardiovascular mortality and the respiratory ER visits in Seoul, Korea. Furthermore, the shape of the concentration-response (C-R) relation of ozone showed non-linearity with cardiovascular mortality and linear relationships with other health outcomes: respiratory mortality, cardiovascular ER visits and respiratory ER visits. This is the first study of exploring the effect of ozone on mortality and ER visits simultaneously in Seoul, Korea and also the first study of examining the shape of the C-R relationship of ozone on ER visits.

The findings of the shape of the association with ozone on cardiovascular and respiratory mortality were consistent with the most recent study (Bae, Lim et al. 2015) about ozone. This previous study found non-linear relationships with non-accidental mortality and cardiovascular mortality, while suggesting a linear relationship with respiratory mortality. Besides, 9 out of 13 Korea major cities had non-linearity between ozone and non-accidental mortality and 6 cities among those were observed to have a threshold, which means that even Korea cities did not show consistent results. Other previous studies in Korea investigated the existences of the threshold and observed to have non-linear relationship with ozone during the summer in 1995- 1999 and with previous day's ozone level (Hong, Leem et al. 1999, Kim, Lee et al. 2004). In addition, a study in U.S. examined the existence of the threshold in 9 U.S. cities and found that unlike cardiovascular disease, respiratory mortality showed linear relationship with ozone (Stylianou and Nicolich 2009). Our study also showed linear relationship for respiratory mortality. As the effect of ambient temperature is mostly known as non-linearity, non-linear relationship with ozone is likely to be supported due to the fact that ozone is highly correlated with temperature. However, our results showed non-linear relationship only with cardiovascular mortality. This is because the impact of ozone on respiratory diseases could trigger ER visits, while leading to death for cardiovascular diseases. The shapes of the relationship with cardiovascular ER visits and respiratory mortality were not statistically significant, so the shape of the relationship with cardiovascular diseases should be considered as non-linear and with respiratory disease as linear association. The mechanism of ozone on the respiratory system is known to be similar to those of other air pollutants, but the mechanism of ozone on the circulatory system is still under investigation (Yang and Ballinger 2005). The exposure to ozone directly affects the respiratory system, while second order inflammatory reaction or oxidative damage to red blood cells could affect the circulatory system. Since multiple mechanisms are involved in mediating inflammatory responses to ozone exposure, the effects of ozone vary depending on the health outcomes.

Opposed to our results, a previous study showed significant effects of ozone on non-accidental, cardiovascular and respiratory mortality through the whole year and during the cold season, but not during the warm season (Zhang, Huang et al. 2006). However, most of the previous studies had significant results during summer or the warm season. For 36 major cities in U.S., the study found the risk of COPD and pneumonia hospital admission were increased by ozone during the warm season, but not during the cold season (Medina-Ramón, Zanobetti et al. 2006). Moreover, a number of studies focused on mortality for cardiovascular diseases whereas emphasizing on ER visits or hospital admissions for respiratory diseases. One of the studies in Spain found the effect of ozone on daily emergency admissions was increased in cardiovascular and heart diseases (Ballester, Rodriguez et al. 2006). The reason of focusing on certain health outcome might be that cardiovascular diseases are more related to severe consequences such as death, while respiratory diseases are less related to mortality but rather lead to ER visits or hospital admissions. In spite of these previous studies, we examined the effect of ozone on both mortality and ER visits and found consistently significant results of ozone effect both on cardiovascular mortality and respiratory ER visits.

Moreover, the Air Quality Index (AQI) by Environmental Protection Agency (EPA) is an index of air quality to protect human health (EPA 2003). AQI was established with the relative higher standard than the thresholds of non-accidental and cardiovascular mortality in our study. Currently in Korea greater than 120 ppb of daily 1-hour ozone concentration stands for 'ozone watch', greater than 300 ppb of ozone represents 'ozone warning', and greater than 500 ppb represents 'ozone advisory', while the thresholds of non-accidental and cardiovascular mortality were 38.51 ppb and 26.508ppb of daily 8-hour ozone concentration (환경청 2004). Even with different metrics of daily ozone concentration, the daily 8-hour maximum ozone concentration had a threshold of 42.192 ppb for non-accidental mortality, which corresponds with the 'moderate' air quality level (Schwarzenegger 2005). Even when sensitive population could only be affected at around the threshold, the current AQI for ozone and Korea ozone warning system have a loose standard. Based on our study, the daily 1-hour ozone concentration didn't exceed 151 ppb during 2000 and 2013, which is the baseline for 'unhealthy' level. But even with less than 151 ppb of daily ozone level, the whole population has high possibility to get ozone-related symptoms.

However, in this study, we have some limitations. First, currently the mechanisms of ozone on health are not clearly known. So the reason for having different shapes of the relationship between ozone and health outcomes could not be explained. Further studies are needed to investigate how low and high ozone concentrations affect on human health. Second, subcategories of cardiovascular diseases could not be used in the analyses due to lacking cases, especially for mortality. So it was difficult to find the relationship with ozone. Third, air pollutants and weather variables were measured at the background monitoring stations and it might not be the true exposure of ozone on individual levels.

Despite these limitations, our results lead to the conclusion that ground-level ozone has the effect both on mortality and morbidity. In order to please the citizens with the pleasant and clear air for living and to reduce the burden of health effect of pollutions in Seoul, the government should pay particular attention to air pollutants.

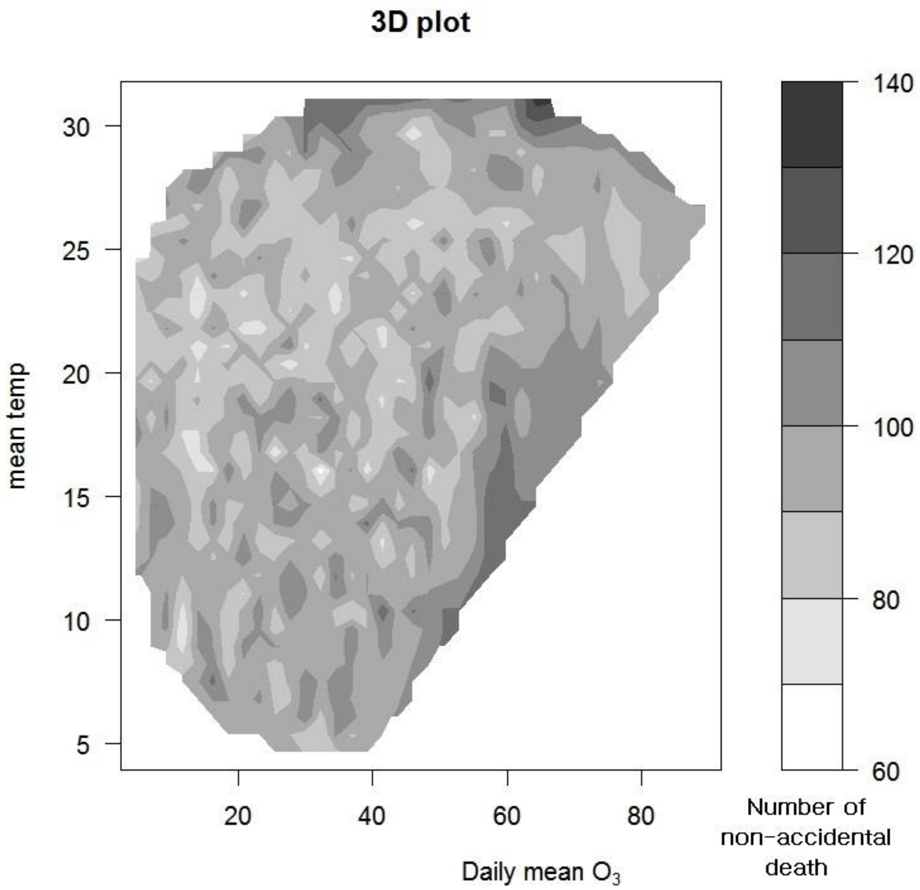
Appendix

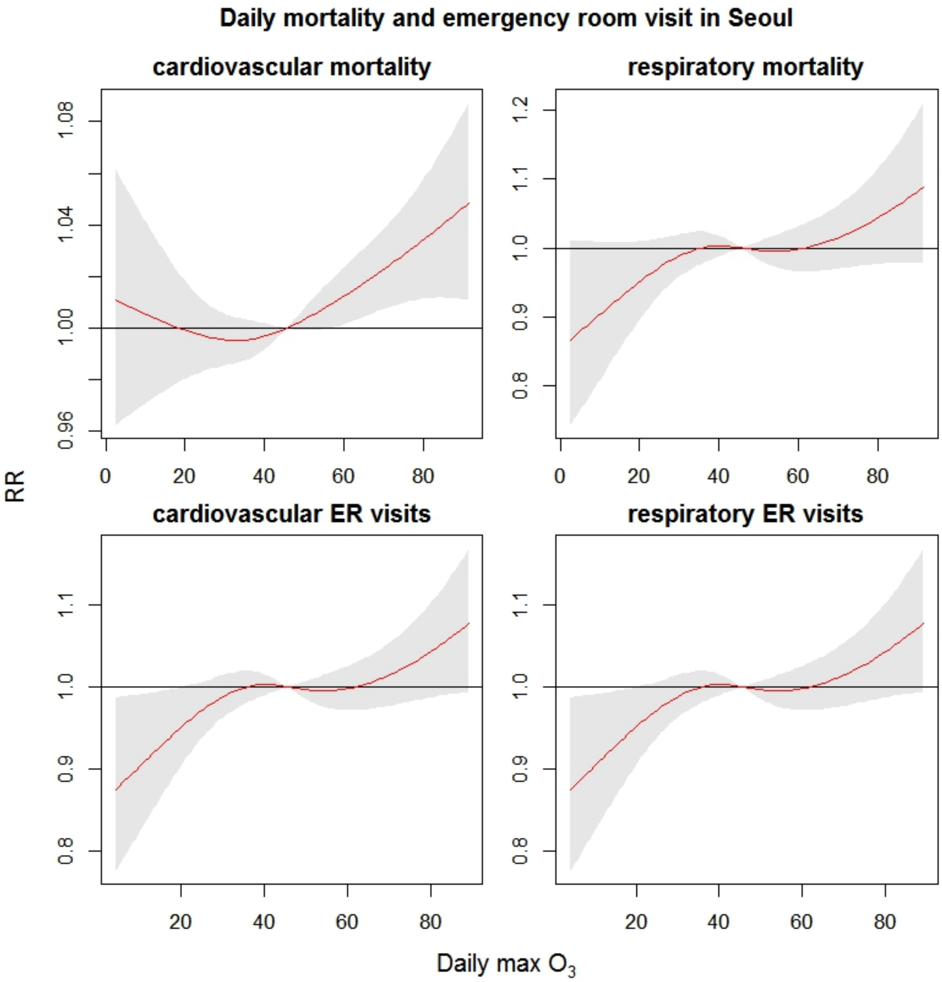
Appendix 1. Pearson correlation among ozone and environmental variables in Seoul, Korea

	O_3[a]	temperature	humidity	pm_{10}
O_3	-	0.475	-0.209	-0.012
temperature	-	-	0.408	-0.13
humidity	-	-	-	-0.074
pm_{10}	-	-	-	-

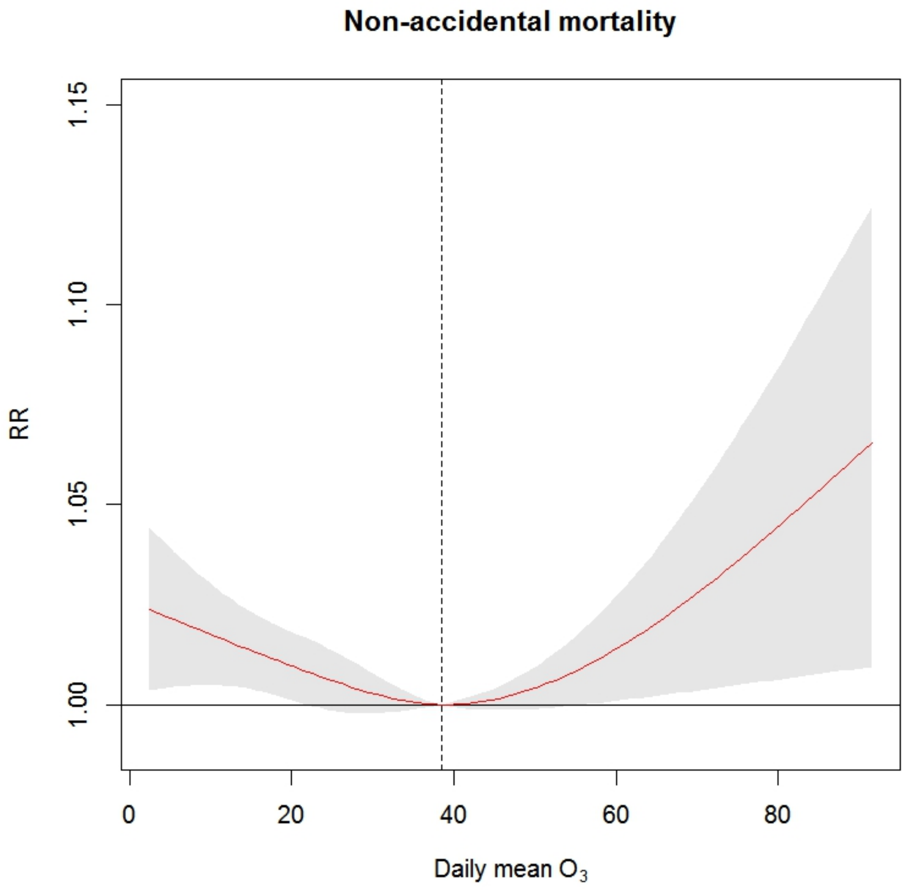
a: daily 8-hour average (9 am-5 pm)

Appendix 2. 3D plot of daily mean ozone, daily mean temperature and daily number of non-accidental mortality

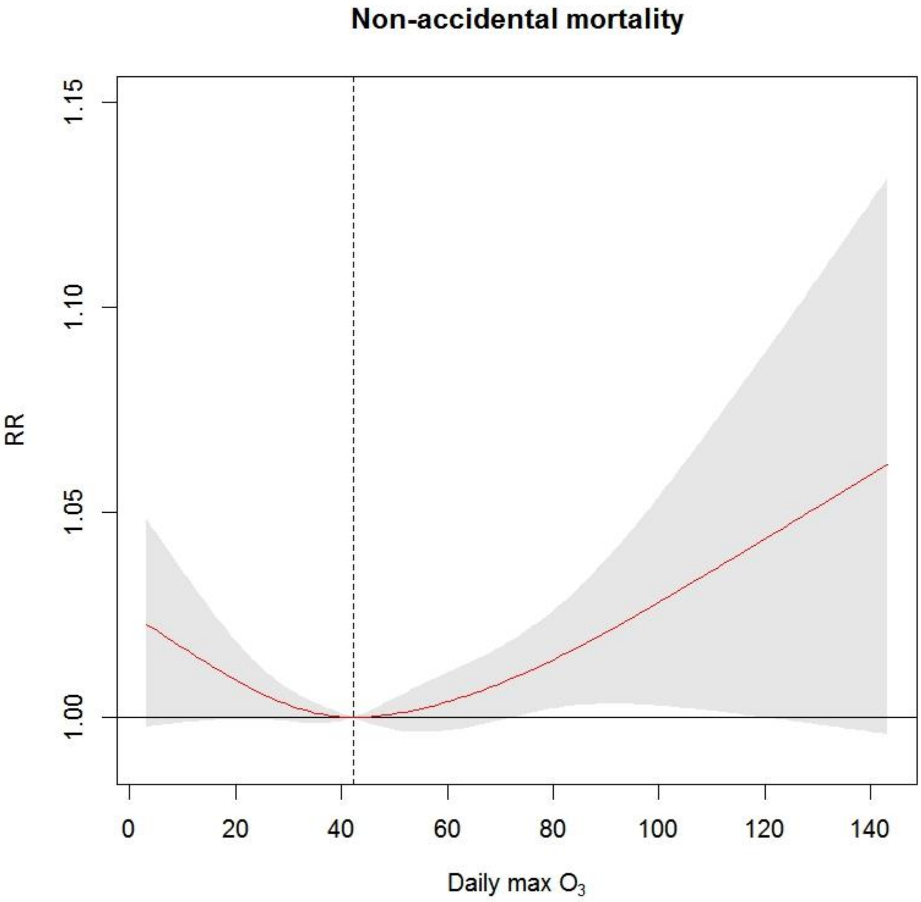




Appendix 3. The estimated effect of daily maximum ozone (lag0-1) on cardiovascular and respiratory ER visits (2010-2013) with natural spine model Seoul, Korea



Appendix 4. The estimated effect of daily mean ozone (lag0-1) on non-accidental mortality (2000-2013) in Seoul, Korea



Appendix 5. The estimated effect of daily maximum ozone (lag0-1) on non-accidental mortality (2000-2013) in Seoul, Korea

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국문초록

서울에서 오존이 심혈관계 질환 및 호흡기계 질환 사망과 응급실 방문에 미치는 영향

황신하

보건학과 보건통계학전공

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연구배경: 대기 중 오존은 건강에 영향을 미치는 것으로 알려져 있다. 많은 선행연구에서 오존과 사망과의 관계는 유의한 양의 관계가 나타났다. 하지만 오존과 사망과의 비선형적 관계 및 역치 존재 여부에 대한 연구 결과는 일괄적이지 않다. 반면, 오존과 응급실 방문과의 관련성에 대한 연구는 상대적으로 드물며, 응급실 방문에서의 농도-반응 관련성을 파악한 국내 연구는 없다.

목적: 본 연구는 서울에서 오존이 심혈관계 질환 및 호흡기계 질환에 미치는 단기적 영향을 알아보고자 하며 사망과 응급실 방문에서의 오존과의 관계를 파악하고자 한다.

연구방법: 본 연구는 오존의 영향을 추정하기 위해 일반화 선형 모형을 이용한 시계열 분석을 수행하였다. 오존과의 관련성이 비선형인지

알아보기 위해 natural spline model을 이용하여 모양을 파악하였고 natural spline model과 linear model의 QAIC를 비교하였다. 농도-반응 관련성과 QAIC 결과를 바탕으로 health outcome에 따라 적합한 모형을 선정한 다음 오존에 따른 초과 상대 위험도(ERR)를 추정하였다. 또한 연령별 및 성별에 따른 분석과 세부 호흡기계 질환에 따른 분석을 시행하였다.

결과: 오존과 심혈관계 질환 사망은 비선형적 관련성을 보인 반면 호흡기계 질환 사망은 직선적 관계로 나타났다. 응급실 방문에서는 심혈관계 질환과 호흡기계 질환에서 오존과의 관계가 선형적이었다. 초과 상대 위험도는 심혈관계 질환에 의한 사망 (ERR=1.36%, 95% CI: 0.422 - 2.311), 호흡기계 질환에 의한 응급실 방문 (1.869%, 95% CI: 0.739 - 3.011), 천식에 의한 응급실 방문 (6.267%, 95% CI: 3.846 - 8.744), 만성폐쇄성 폐질환에 의한 응급실 방문 (3.707%, 95% CI: 1.673 - 5.781), 폐렴에 의한 응급실 방문 (3.150%, 95% CI: 1.847 - 4.469)에서 유의한 결과가 나타났다. 또한, 심혈관계 질환에 의한 사망과 응급실 방문에서 65세 이상 (1.170%, 95% CI: 0.098 - 2.258, 1.769%, 95% CI: 0.340 - 3.218)에서 더 높은 위험도가 나타났으며, 호흡기계 질환에서도 65세 이상 (1.845%, 95% CI: 0.316 - 3.397)과 남성 (1.884%, 95% CI: 0.735 -3.047)에서 위험도가 유의하게 더 크게 나타났다.

결론: 본 연구는 오존과 심혈관계 질환의 비선형적 관계에 대한 증거를 제공하였고, 오존과 응급실 방문과의 관련성은 선형으로 관찰되었다. 또한, 오존이 호흡기계 질환에 의한 응급실 방문에 영향을 미치는 것으로 나타났으며, 심혈관계 질환은 사망에 영향을 미치는 것으로 관찰되었다.

주요어 : 오존, 사망, 응급실방문, 심혈관계질환, 호흡기계질환, 일반화선형모형
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